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Potential of synchrotron X-ray powder diffractometry for detection and quantification of small amounts of crystalline drug substances in pharmaceutical tablets

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ABSTRACT

The purpose of this study was to develop a sensitive system for detection of crystalline drug substances in intact pharmaceutical tablets by X-ray powder diffractometry (XRPD), using synchrotron X-rays. Fenoprofen calcium dihydrate was used as a model compound. The wavelength and path length of X-rays from synchrotron radiation were optimized in order to maximize the potential of the synchrotron radiation. The optimum wavelength and path length for the measurement of fenoprofen calcium dihydrate were found to be 0.69817 Å and 6.0 mm, respectively, based on theoretical calculations. Under the optimized conditions, a limit of quantification of 0.05% (RSD = 9.4%, $n = 3$) and a limit of detection of 0.02% (RSD = 17.3%, $n = 3$), results which are approximately 10^2 times as sensitive as those obtained using conventional XRPD instruments, were achieved. The technique was also applied to fenoprofen calcium dihydrate detection in intact film-coated tablets, which contained Ti in the coating film, and a limit of detection of 0.02% was again attained.

1. Introduction

It is well known that the crystal form of an active pharmaceutical ingredient (API) is one of the key aspects of drug development because physical properties such as solubility and stability are affected by the crystal form. The crystal form of an API may therefore influence the bioavailability and quality of a drug [1]. The effects of the physical form of the API on the performance, stability, and efficacy of solid dosage forms have been the subject of numerous publications [2,3]. Usually, the physical form of the API in manufacture of the dosage form is well controlled, and the API properties are characterized at an early stage of development. However, processing steps such as milling, granulation, drying, and compression may bring about API phase transformations. In practice, the regulatory guidelines require monitoring of the physical form of the API in the dosage form [4]. However, since solid dosage forms are often complex multicomponent systems, API characterization in the dosage form may be analytically challenging. The problem will be exacerbated if the weight fraction of the API in the final product is low.

Recently, the development of analytical techniques for the characterization of pharmaceutical solids has attracted considerable attention [5,6]. Raman spectroscopy and principal components analysis were used for the determination of ranitidine hydrochloride and carbamazepine, achieving detection limits of about 2% in both studies [7,8]. When solid-state NMR was employed to evaluate bambuterol tablets, the API detection limit was estimated to be about 0.5% [9]. Several techniques, including Raman, NIR, solid-state NMR, and DSC, have been developed and compared with X-ray powder diffraction (XRPD) methods [10–14]. Although it depends on the properties of the drug and the purpose of the method development, XRPD has been a useful technique for API characterization [15]. Quantitative XRPD methods have been established for the detection of clopidogrel bisulfate polymorphs and olanzapine polymorphs. The limits of detection for these methods were 1.0–1.5% and 0.40%, respectively [16,17]. A non-destructive XRPD method has recently been developed and applied to API characterization in pharmaceutical film-coated tablets [18,19].

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Synchrotron radiation is a powerful tool for the characterization of pharmaceutical materials. The advantage of synchrotron radiation is the availability of arbitrary wavelengths by using a large-scale double-crystal monochromator, as well as its high intensity with low dispersion. The crystal structures of pharmaceutical materials such as D-mannitol hemihydrate, carnidazole, and mebendazole have been determined using high-resolution synchrotron radiation [20–22]. A sensitive detection system for crystalline sucrose in amorphous materials has also been developed using synchrotron radiation as a high-intensity X-ray source [23]. The limit of detection achieved was 0.2%, which is a considerable improvement on the reported value of ~1% obtained using conventional XRPD.

The goal of this paper is to develop a sensitive detection system for crystalline APIs in pharmaceutical tablets using synchrotron X-rays. Fenoprofen calcium dihydrate was used as a model compound. In the transmission geometry, the diffracted X-ray intensity depends on the path length of the sample. If the sample is too thin, the diffracted intensity is low since the sample volume subjected to X-ray diffraction is low, while the diffracted intensity is also low if the sample is too thick due to the absorption of X-rays by the sample. The attenuation of X-ray depends on the attenuation coefficient of the sample, which is a function of the energy (wavelength) of the X-rays. Therefore, both the path length and the wavelength of the X-rays should be optimized in order to attain a sensitive detection system. The method developed in this study was also applied to the detection of a crystalline API in intact film-coated tablets. Generally, the characterization of intact film-coated tablets by XRPD poses some unique challenges because X-rays are attenuated by metals such as Ti and/or Fe contained in the coating film. Taking advantage of synchrotron X-ray as a high-intensity X-ray source, the method was applied to the non-destructive detection of fenoprofen calcium dihydrate in film-coated tablets containing Ti in the coating film.

2. Materials and methods

2.1. Materials

Fenoprofen calcium dihydrate was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) and used as received. Pharmatose-200 (lactose for direct compression) was obtained from DMV International (Veghel, The Netherlands). Talc, magnesium stearate, hypromellose and Dilactose-S (lactose for direct compression) were purchased from Hayashi-Kasei (Osaka, Japan), Merck KGaA, (Darmstatd, Germany), Shin-Etsu Chemical (Tokyo, Japan) and Freunt Corporation (Tokyo, Japan), respectively.

2.2. Fenoprofen tablets

For the preparation of 10% fenoprofen calcium dihydrate in lactose, 2.0 g of fenoprofen calcium dihydrate and 18.0 g of Pharmatose-200 were mixed for 5 min at 1000 rpm using a mixer. To 2.0 g of the mixed powder, 18.0 g of Phamatose-200 was added and then mixed to make 1% fenoprofen calcium dihydrate in lactose. For example, in order to prepare tablets containing 1% fenoprofen calcium dihydrate, 5.0 g of 10% fenoprofen calcium dihydrate in lactose, 0.25 g of talc, 0.25 g of magnesium stearate, and 44.5 g of Dilactose-S were mixed for 5 min at 1000 rpm using a mixer. A Minipress-MII desktop-type tableting machine (Riva, Aldershot, Hampshire, UK), with a tableting pressure of 6.5 N, was used to prepare the tablets. The tablet weight was 120 mg, with a tablet diameter of 6.0 mm and a thickness of 3.0 mm. Tablets containing 0.02–0.5% fenoprofen calcium dihydrate were also prepared. Similarly, 1% fenoprofen calcium dihydrate tablets of various tablet thicknesses (2.0–8.0 mm) were prepared, using the same formulation, by changing the tablet weight. Fenoprofen film-coated tablets were prepared by coating fenoprofen tablets with a film containing hypromellose (62.5%), talc (12.5%), titanium dioxide (TiO_2; 12.5%), and PEG6000 (12.5%) using an aqueous film-coating process.

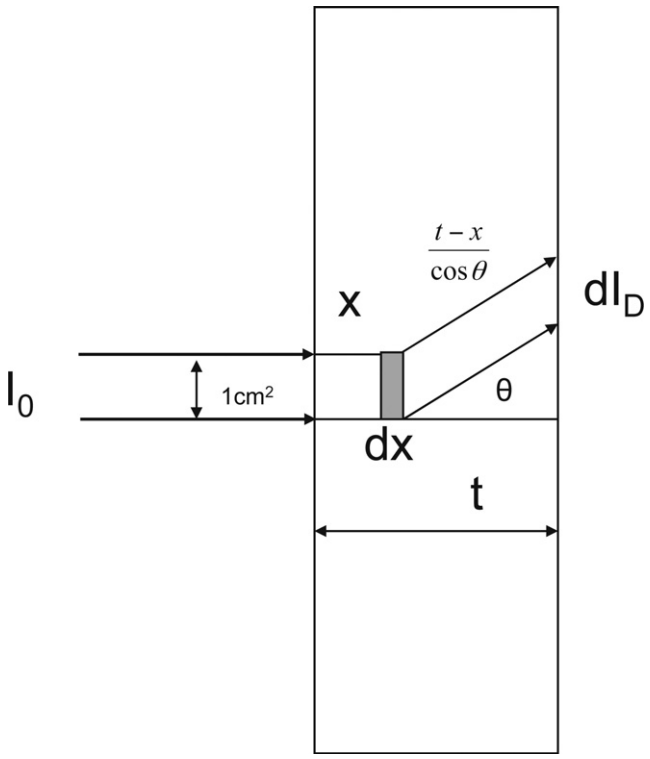

Fig. 1. Schematic representation of diffraction of X-rays in the transmission geometry.

2.3. XRPD measurements using synchrotron radiation

XRPD experiments using synchrotron radiation were performed at 300 K on a beamline BL19B2 at SPring-8 (high-resolution-type Debye–Scherer camera equipped with a curved imaging plate detector). For these experiments, SPring-8 standard double-crystal monochromator and two mirror-systems were used to monochromatize wavelengths between 0.65 and 1.1 Å continuously. The beam size was 3 mm (horizontal) and 0.3 mm (vertical). A glass capillary was glued to the center of the tablets to serve as a rotating wheel axis, and then fixed to the goniometer head with height adjustment. The measurements were performed while rotating the tablet at 60 rpm, with the incident direction taken as the tablet radial direction (perpendicular to the rotating wheel axis) so that synchrotron radiation irradiated an entire tablet [26]. The exposure time was 5 min (optimization experiment) or 20 min (quantitative measurement). The diffracted X-rays were detected using an imaging plate. The exposed imaging plates were allowed to fade for 10 min, and then the diffracted intensity was read with a scanner and dedicated software. The results were analyzed using commercially available software (JADE 6.0, Materials Data, Inc., Livermore, CA, USA).

2.4. Calculation of optimum sample thickness

In the transmission geometry, as shown in Fig. 1, a change in the diffracted intensity, I_D, from a layer of thickness dx located at a depth x is given by Eq. (1) [24]:

$$dI_D = abI_0 e^{-\mu(x+(t-x/\cos\alpha))}dx \quad (1)$$

where I_0 is the incident beam intensity and is 1 cm^2 in cross-section, a is the volume fraction of the specimen particles correctly oriented for diffraction, b is the fraction of incident radiation diffracted by a unit sample volume, μ is the linear attenuation coefficient of the sample, t is the thickness of the sample, and α is the diffracted X-ray position (2θ).

In the low 2θ range, α can be regarded as 0, therefore Eq. (1) is approximated to Eq. (2):

$$dI_D = abI_0 e^{-\mu t}dx \quad (2)$$

Eq. (3) is obtained by the integration of Eq. (2):

$$I_D = \int_0^t dI_D dx = abI_0 e^{-\mu t}\int_0^t dx = abtI_0 e^{-\mu t} \quad (3)$$

After differentiating Eq. (3) by the thickness t of the sample, Eq. (4) is obtained:

$$\frac{dI_D}{dt} = abI_0\frac{dte^{-\mu t}}{dt} = abI_0\left(t-\frac{1}{\mu}\right)e^{-\mu t} \quad (4)$$

In Eq. (4), $t = 1/\mu$ gives $dI_D/dt = 0$, therefore I_D exhibits the maximum value at $t = 1/\mu$. In other words, the diffracted intensity has the maximum value when the thickness of the sample is $1/\mu$.

3. Results

3.1. Optimization of experimental conditions

In order to develop a sensitive detection system using synchrotron radiation, both the X-ray wavelength and the sample thickness should be optimized. As a first step, a wavelength of 0.69817(5) Å was selected, since the maximum intensity was obtained at around $\lambda = 0.69817$ Å (17.7 keV) under our tuning conditions.

As mentioned above, the optimum thickness of the sample is $1/\mu$, thus the linear attenuation coefficient (μ) of the sample should be known. The linear attenuation coefficient is the product of the mass attenuation coefficient (μ/ρ) and the density of the sample (ρ). The mass attenuation coefficient of the sample can be calculated based on the weight fraction of the components in the formulation and the mass attenuation coefficient of each element. Although the mass attenuation coefficients of the elements at 0.7107 Å (Mo Kα), 0.6323 Å (Mo Kβ1), and 0.5608 Å (Ag Kα) are available in the literature [25], the values at 0.69817 Å are not known. The mass attenuation coefficients at 0.69817 Å were therefore calculated by interpolation, using the regression line ($r \geq 0.99$ for all the elements) of the above data. The calculated linear attenuation coefficient of the sample is 1.60 cm^{-1}, and the calculated optimum sample thickness is 0.63 cm, when the X-ray wavelength is 0.69817 Å.

3.2. XRPD patterns of fenoprofen tablets

XRPD patterns of lactose, fenoprofen calcium dihydrate, a placebo tablet, and a 0.5% fenoprofen tablet were measured using synchrotron radiation of wavelength 0.69817 Å. As shown in Fig. 2, fenoprofen calcium dihydrate exhibited diffraction peaks at 2.9–3.0° (2θ), and lactose had a diffraction peak at 3.7° (2θ). Although the peaks at 2.9–3.0° (2θ) were not separated from each other, these peaks were clearly separated from the lactose peak, thus these peaks can be used as the fenoprofen calcium dihydrate characteristic peak and the internal standard peak, respectively. For the 0.5% fenoprofen tablet, crystalline fenoprofen calcium dihydrate peaks were detected at 2.9–3.0° (2θ), while the placebo tablet did not exhibit the peaks.

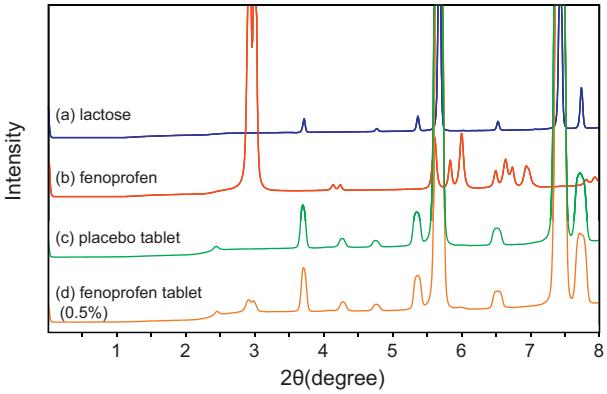

Fig. 2. XRPD patterns of (a) lactose, (b) fenoprofen calcium dihydrate, (c) placebo tablet without fenoprofen calcium dihydrate, and (d) tablet containing 0.5% fenoprofen calcium dihydrate.

3.3. Optimization of sample thickness

In order to confirm the optimum sample thickness for X-rays of wavelength 0.69817 Å, the diffraction intensities (peak areas) of fenoprofen tablets of various sample thicknesses were measured. Fenoprofen tablets of thickness 2.0–8.0 mm, containing 1% fenoprofen calcium dihydrate, were used for this purpose. Fig. 3 shows the plot of the diffracted intensity as a function of the sample thickness. Although the intensity did not show a distinctive peak, the experimental data were consistent with the theoretical calculation (solid line in Fig. 3).

3.4. Optimization of X-ray wavelength

After optimization of the sample thickness for X-rays of wavelength 0.69817 Å, the diffraction intensities of fenoprofen calcium dihydrate in tablets as a function of X-ray wavelength were determined in order to confirm that 0.69817 Å is the optimum wavelength for 6.0 mm samples. A tablet of thickness 6.0 mm, containing 0.5% fenoprofen calcium dihydrate, was used for the measurements. The theoretical values could not be calculated since the incident X-ray beam intensity is not constant over the range 0.65–1.1 Å. As shown in Fig. 4, the plot of the fenoprofen calcium

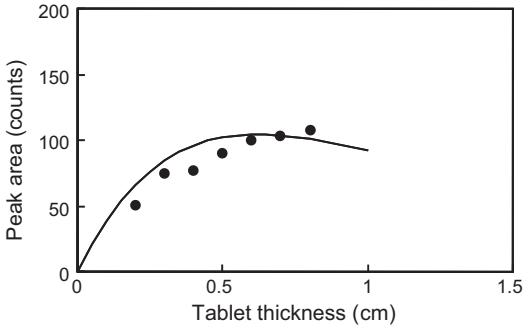

Fig. 3. Plot of the integrated peak intensity of fenoprofen calcium dihydrate as a function of tablet thickness.

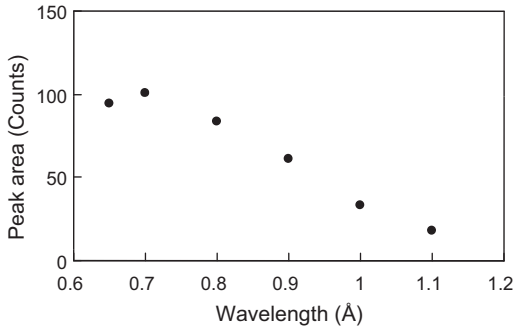

Fig. 4. Plot of the integrated peak intensity of fenoprofen calcium dihydrate as a function of X-ray wavelength.

dihydrate peak intensity as a function of X-ray wavelength exhibited the highest value at around 0.70 Å.

These results demonstrated that the experimental data for the sample thickness and X-ray wavelength were consistent with theoretical calculations. The experimental conditions for the sensitive detection of fenoprofen calcium dihydrate in tablets were therefore determined to be an X-ray wavelength of 0.69817 Å, and a sample thickness of 6.0 mm.

3.5. Quantitative XRPD of fenoprofen calcium dihydrate in tablets

Using the experimental conditions described above, the limit of detection of fenoprofen calcium dihydrate in tablets was investigated. The integrated peak intensities of the fenoprofen calcium dihydrate diffraction peaks were determined. Measurements were performed on tablets containing 0.02–0.5% fenoprofen calcium dihydrate. The X-ray wavelength was 0.69817 Å, based on the results of the optimization studies described in the previous section. The dimensions of the tablets used in this study were a thickness of 3.0 mm and a diameter of 6.0 mm, which is a normal size for pharmaceutical tablets. Therefore, the tablet was vertically mounted on the sample holder with the circular face of the tablet (width: 3.0 mm) directed to the X-rays, so that the X-ray beam could pass through the tablet along the tablet diameter; the path length of the X-ray was therefore 6.0 mm. The tablet was rotated during the measurements (60 rpm), so the entire tablet was exposed to the X-rays, and a signal from the entire tablet was obtained. Since the entire tablet was exposed to X-rays, and the sample was rotated during the measurements, the effect of preferred orientation was not considered to be significant.

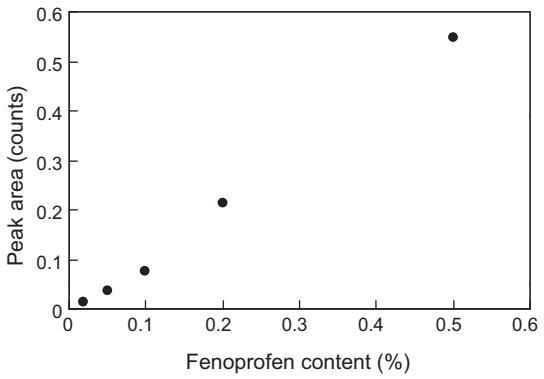

Fig. 6. Plot of the ratio of fenoprofen calcium dihydrate peak area to the internal standard as a function of fenoprofen calcium dihydrate concentration in the formulation.

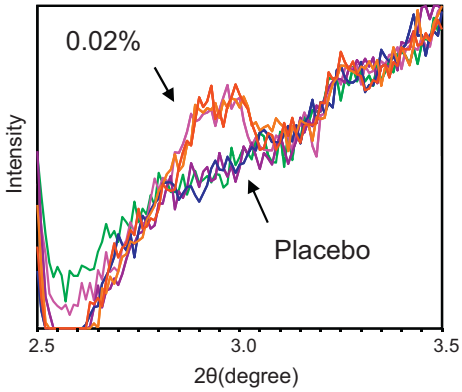

Fig. 7. Overlay plot of XRPD patterns of 0.02% fenoprofen tablets ($n = 3$) and placebo tablets ($n = 3$).

The tablet diffraction patterns are shown in Fig. 5. The diffraction peak of lactose (3.7° 2θ) was used as an internal standard. The ratio of the peak area at 2.9–3.0° (2θ) to the internal standard, as a function of the spiked fenoprofen calcium dihydrate content in tablets, yielded a linear relationship ($r = 0.998$) in the range 0.02–0.5% (Fig. 6). The tablets containing 0.02% fenoprofen calcium dihydrate exhibited the distinctive fenoprofen calcium dihydrate diffraction peak, as shown in Fig. 7. The RSD values at 0.02% and 0.05% were 17.3% ($n = 3$) and 9.4% ($n = 3$), respectively. The limit of detection of fenoprofen calcium dihydrate in the tablets

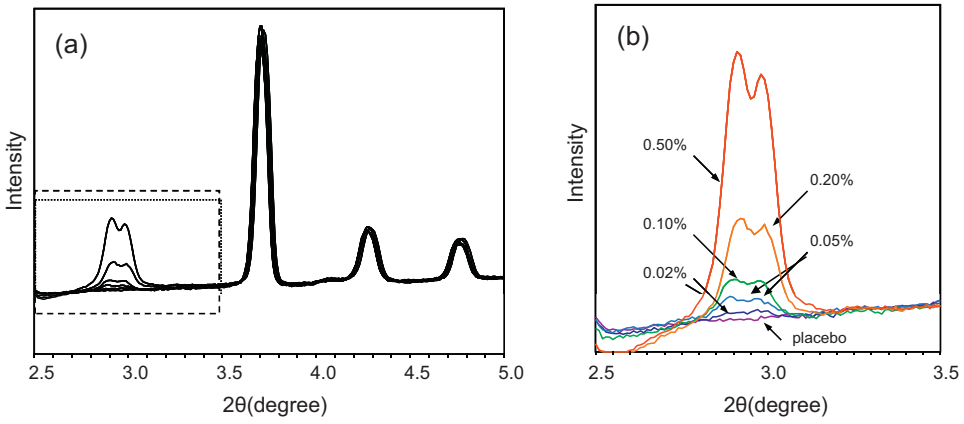

Fig. 5. (a) XRPD patterns of fenoprofen tablets. The concentrations of fenoprofen calcium dihydrate in the formulation are 0.50%, 0.20%, 0.10%, 0.05%, 0.02%, and placebo. (b) XRD patterns between 2.5° and 3.5° (2θ) shown on expanded axes.

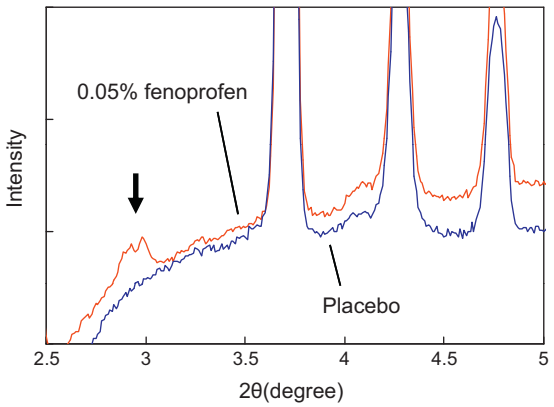

Fig. 8. XRPD patterns of 0.05% fenoprofen film-coated tablet and placebo film-coated tablet. The fenoprofen calcium dihydrate peak is indicated by an arrow.

was therefore estimated to be 0.02%, and the limit of quantification was estimated to be 0.05%.

3.6. Detection of fenoprofen calcium dihydrate in film-coated tablets

This technique was also applied to the detection of fenoprofen calcium dihydrate in intact film-coated tablets. Fenoprofen film-coated tablets containing 0.02–0.5% fenoprofen calcium dihydrate were non-destructively subjected to measurements under the same experimental conditions. The XRPD patterns of a film-coated tablet containing 0.05% fenoprofen calcium dihydrate and of a placebo tablet are shown in Fig. 8. Although a slight increase was seen in the diffraction pattern (due to the X-ray scattering by Ti in the coating film), other materials in the coating film did not interfere with the fenoprofen calcium dihydrate peaks. Fig. 8 shows that the technique clearly detected 0.05% fenoprofen calcium dihydrate in a film-coated tablet. The ratios of the fenoprofen calcium dihydrate peak to the internal standard (lactose peak) were on the same regression line as that of the core tablet. The limit of detection for the film-coated tablets was also 0.02%.

4. Discussion

The physical form of the API in the dosage form is important since it affects the performance and quality of the drug. From a regulatory perspective, while the importance of monitoring the physical form of the API in the dosage form is well recognized, it is analytically challenging. As a result, such characterization studies are required only when it is "technically possible". Quantitative XRPD methods have been developed to monitor the physical form of APIs in tablets, however the sensitivity using conventional XRPD instruments is not sufficient. Synchrotron radiation is a powerful tool for this purpose because of its high intensity. We have applied the XRPD method, using synchrotron radiation, to the sensitive detection of drug substance in intact tablets. In order to maximize the potential of the synchrotron radiation, the wavelength and path length of the X-rays were optimized, based on theoretical considerations. As a result, a limit of detection of 0.02% for fenoprofen calcium dihydrate in tablets was achieved. This technique has the potential to detect a 2% phase transition in 100 mg tablets containing 1 mg of a drug substance in the formulation (=0.02% crystallinity in the formulation).

5. Conclusion

A sensitive system for the detection of crystalline fenoprofen calcium dihydrate in pharmaceutical tablets was developed. Synchrotron radiation was used as a high-intensity X-ray source. The wavelength and path length of the X-rays were optimized, in order to maximize the potential of the synchrotron radiation as a high intensity X-ray source, based on theoretical considerations of the transmission geometry. The suitability of the measurement conditions was confirmed experimentally. Using the optimized measurement conditions, a limit of detection of 0.02% for fenoprofen calcium dihydrate in tablets, a value which is approximately 10^2 times as sensitive as that obtained using conventional XRPD instruments, was achieved. The technique was also applied to fenoprofen calcium dihydrate detection in intact film-coated tablets containing Ti in the coating film, and a limit of detection of 0.02% was attained.

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